

AMENDMENTS TO THE SPECIFICATION

Please amend the following paragraphs accordingly

Page 3, lines 8 and 16,

an aromatic group optionally having one or more substituents, the aromatic ring having optional nitrogen, sulfur or oxygen, wherein the substituent is; hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; or linear or cyclic C₁-C₆ alkyl optionally having one or more substituents, the alkyl having an optional nitrogen, sulfur or oxygen linkage and the substituentsubstituent of the alkyl being: hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; an aromatic group optionally having one or more substituents selected from the group consisting of hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; amido; dioxoisoindole; and a sulfonylamino having an aromatic group substituted with hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamido, alkanesulfonyl or amido; an aromatic group optionally having one or more substituents selected ~~form~~from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamide, alkanesulfonyl and amido, the aromatic ring containing nitrogen, sulfur or oxygen; or a cyclic C₃-C₈ alkyl optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido; or

Page 3, lines 31 and 37

Among the compounds of formula (I) of the present invention, the preferred are:

those wherein n, R¹, R² and R³ have the same ~~meaning~~meanings as defined previously;
R⁴ and R⁵ are each independently hydrogen;
C₁-C₄ alkyl optionally having one or more substituents selected from the group consisting of OH, NH₂, NO₂, and an aromatic group, the aromatic group optionally having one or more substituents selected from the group consisting of OH, C₁-C₄ alkyloxy, NH₂, NO₂, methanesulfonylamino, ethanesulfonylamino, ~~tolunensulfonylaminotoluenesulfonylamin~~ and dioxoisoindole; cyclic C₃-

Page 4, lines 3-7, 16, 25, 29, and 32

C₈ alkyl optionally having one or more substituents selected from the group consisting of OH, NH₂ and NO₂; C₁-C₄ alkyl carrying a morpholine or ~~exopyrrolidine~~oxopyrrolidine group which is optionally substituted with OH, NH₂, NO₂ or -O-; C₁-C₄ alkyl or C₁-C₄ aminoalkyl carrying a ~~pyrrole~~pyrrolyl, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, isoxazole, oxazole, ~~isothiazole~~isothiazole, ~~tiazolidine~~thiazolidine, tiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,2,5-thiodiazole~~thiadiazole~~, 1,2,3-thiodiazole~~thiadiazole~~, 1,3,4-oxadiazole, 1,3,4-thiodiazole~~thiadiazole~~, pyridine, pyrimidine or triazine group which is optionally having one or more substituents selected from the group consisting of Cl, OH, NH₂, NO₂, C₁-C₄ and phenyl; cyclic C₃-C₈ alkyl optionally having one or more substituents selected from the group consisting of OH, NH₂ and NO₂;

an aromatic group optionally having one or more substituents selected from the group consisting of OH; NH₂; hydroxyalkyl; aminoalkyl; NO₂; and a C₁-C₄ alkyl group optionally having one or more substituents selected from the group consisting of OH, NH₂, NO₂,

methanesulfonylamino, ethanesulfonylamino, ~~toluenesulfonylaminotoluenesulfonylamino~~,

dioxoisoindole and thiophensulfonylamino; or

form, together with the -N-(CH₂)_n- moiety to which they are attached, a nitrogen heterocycle optionally having one or more substituents selected from the group consisting of OH, NH₂ and NO₂, the heterocycle containing 1 to 3 nitrogen, sulfur or oxygen atom.

In the present invention, the compounds of formula (I) as the below are most preferred: those wherein n, R¹, R² and R³ have the same ~~meaning~~ meanings as defined previously; R⁴ and R⁵ are each independently hydrogen;

C₁-C₄ alkyl optionally having one or more substituents selected from the group consisting of OH, NH₂, NO₂, morpholine, nitropyridineamino, pyridine, ~~oxopyrrolidinoxopyrrolidine~~, imidazole optionally having a Cl, CH₃ or phenyl substituent; and phenyl optionally having one or more substituents selected from the group consisting of OH, NH₂, methoxy, NO₂, methanesulfonylamino, ethanesulfonylamino, ~~toluenesulfonylaminotoluenesulfonylamino~~ and dioxoisoindole;

Page 5, line 2

NH₂, NO₂, methanesulfonylamino, ethanesulfonylamino,
~~toluenesulfonylaminotoluenesulfonylamino~~, dioxoisoindole or thiophensulfonylamino substituent; or

Page 15, lines 4-5

wherein, p-TSA is *p*-toluenesulfonic acid, DMF is dimethylformamide, THF is tetrahydrofuran, TFA is trifluoroacetic acid, EDCI is ethyl-dimethylaminopropyl-carbodiimide

hydrochloride, DMAP is 4-dimethylaminopyrdine, HOBr is N-
~~hydroxybezotriazole~~hydroxybenzotriazole, n, R¹, R², R³, R⁴ and R⁵ have the same meaning
meanings as defined previously.

Page 16 , lines 21 and 36

As shown in Scheme II, the compound of formula (Ib) can be prepared by reacting 3-amino-4-methoxy benzoic acid (compound II) and an alcohol (e.g., methanol or ethanol) to obtain compound (III), adding p-toluenesulfonic acid, benzene and 4-nitrobenzonitrile nitrobenzonitrile thereto, refluxing the mixture at 80 to 200 °C, adding NaOCl thereto at room temperature and purifying by silica gel column chromatography to obtain compound (XI); dissolving the compound (XI) thus obtained in an organic solvent, adding an aqueous alkali solution (e.g., Na₂CO₃ solution) thereto, refluxing the mixture and purifying by silica gel column chromatography to obtain compound (XII); dissolving the compound (XII) thus obtained in an alcohol, adding Pd/C thereto and refluxing the mixture to obtain compound (XIII); dissolving the compound (XIII) thus obtained in an organic solvent, adding a base (e.g., CsCO₃, Na₂CO₃, NaHCO₃, K₂CO₃ or KHCO₃), 2-chloroethylmorphine and potassium iodide thereto and stirring the mixture at room temperature to obtain compound (XIV); dissolving the compound (XIV) obtained thus in an organic solvent, adding an alkali hydrate, stirring the mixture at room temperature to obtain compound (XV); dissolving the compound (XV) thus obtained in an organic solvent, adding 4,5-dichloro-1-(3-aminopropyl)imidazole 4,5-dichloro-1-(3-aminopropyl)imidazole and a coupling agent (e.g., EDCI, DMAP or HOBr), stirring the mixture at room temperature and purifying by silica gel

Page 19, line 15

Anhydrous *p*-toluene sulfonic acid (41.99 g, 220.8 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 and benzonitrile (22.77 g, 220.8 mmol) were added thereto and stirred at 180 °C for 5 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO₃ thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO₄ and concentrated under a reduced pressure. The concentrate was dissolved in 50% methanol and 5% NaOCl (56 Mℓ, 37.65 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO₄ and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent – MeOH/CDCl₃ = 5 : 95, Merck, Silicagel 60) to obtain the title compound (31 g, 25.10 mmol) in a yield of 88%.

Page 21, line 37

Anhydrous *p*-toluene sulfonic acid (41.99 g, 220.76 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 of Preparation Example 1 and 4-chlorobenzonitrile (22.78 g, 165.57 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding 1M NaHCO₃ thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO₄ and concentrated under a reduced pressure. The concentrate was dissolved in 500 ml of 50% methanol and 5% NaOCl (197 Mℓ, 132.46 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with ethyl acetate,

the extract was dried over MgSO₄ and concentrated under a reduced pressure. The resulting residue was purified by silica gel column ehlomatography-chromatography (eluent – MeOH : CDCl₃ = 5 : 95,